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10/580,999	03/12/2007	Julia Y. Ljubimova	67789-586	9455

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,999	LJUBIMOVA ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *14-17, 24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/08/2007; 07/02/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-23, drawn to a drug delivery molecule, in the reply filed on 10/20/2008 is acknowledged. The traversal is on the ground(s) that the technical feature is not the cited polymerized carboxylic acid molecular scaffold, but rather that it is the combination of the polymerized carboxylic acid molecular scaffold with the plurality of biologically active molecular modules. This is not found persuasive because Applicant appears to be referring to the Office Action mailed 02/28/2008, rather than that mailed 08/18/2008. The special technical feature was identified as a polymerized carboxylic acid molecular scaffold complexed to biologically active molecular modules, which is known in the art as evidenced by Kabanov, et al. (U.S. Patent 7,056,532, of record) and by the art cited herein.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election without traverse of **a targeting molecule that promotes penetration of the blood-brain barrier as a targeting molecular module** and of the **prodrug antisense molecule targeting alpha-4-laminin** in the reply filed on 10/20/2008 is acknowledged.

Claims 1-28 are pending. Claims 24-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 14-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-13 and 18-23 are under examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 in that the provisional application, 60/527,300, does not provide support for a targeting molecule that promotes penetration of the blood brain barrier. Therefore, the instant claims are accorded the filing date of the instant application, which is 12/02/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 limit claim 1 by requiring a particular molecular mass (molecular weight). There are at least three different, mutually exclusive ways to describe the molecular weight of a polymer, namely the number average molecular weight (Mn) the weight average molecular weight (Mw) and the volume average molecular weight (Mv) (Odian, 1991, pages 20-23). As discussed in Odian, these three different descriptions of molecular weight are mutually exclusive in synthetic polymers; that is, in synthetic polymers none of the values for Mn, Mw, and Mv can be equal to any other of those values. Because the claims do not specify which type of molecular

weight is being refered to, the artisan would be unable to determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFleur, et al. (10/29/2002, U.S. Patent 6,472,512) and Cammas, et al. (1999, Internat. J. Biol. Macromol., v.25:273-82, item 55 on 11/08/2007 IDS) (Cammas).

The claims are to a drug delivery molecule comprising a polymalic acid scaffold with at least one cell-targeting module and at least one pro-drug module covalently attached to the polymalic acid (claims 1 and 3). The claims are further to the drug delivery molecule wherein the pro-drug module is selected to inhibit expression of tumor-specific proteins (claim 2) or wherein the prodrug is an antisense molecule (claim 20). The claims are further to the drug delivery molecule further comprising polyethylene glycol (PEG) or a fluorescent reporter molecule (claims 9-12). Claim 13 is to the drug delivery molecule wherein the targeting molecule is selected to promote penetration of the blood-brain barrier.

LaFleur teaches biodegradable polymeric drug delivery system wherein the polymer comprises polymalic acid and PEG (Column 151, line 49 to column 152, line 3). The agents (prodrugs) for delivery with the biodegradable polymeric drug deliver system include KDI

antisense oligonucleotides including modified oligonucleotides (column 143, line 58 to column 146, line 62). LaFleur also teaches that the molecular weight (affecting the molecular weight and number of carboxyl groups) and hydrophobicity of the drug delivery system may be modified to obtain the desired drug release (column 152, lines 17-20). LaFleur teaches at column 152, last paragraph, that formulations comprising the KDI compositions and a biodegradable polymer may also include release-rate modification agents such as PEG and pore-forming (membrane-disrupting) agents. The delivery system also includes agents that promote the penetration of the blood-brain barrier (top of column 146). LaFleur teaches that antibodies for cell-targeting may be conjugated to the drug compositions (column 72, lines 7-29). LaFleur does not explicitly teach a drug delivery molecule comprising a polymalic acid molecule having a targeting module and an antisense module and a PEG, membrane-disruption, or fluorescent reporter module covalently attached to it. LaFleur does not explicitly teach the drug delivery molecule wherein the polymalic acid molecule has a molecular weight of at least about 5000 or with at least about 50 free carboxylic acid groups.

Cammas teaches polymalic acid as a drug carrier that has lateral carboxylic acid functions which allow the introduction of a biologically active molecule and targeting moiety by appropriate chemical modifications (p.273, second column). Cammas also teaches polymalic acid polymers having alkyl pendant groups, lateral functional groups, and biologically active molecules as pendant groups and that the lateral chemical functions can be modified and adapted to requirements (paragraph spanning pp.273-4). Cammas teaches that polymalic acid polymers can be obtained that have one or several pendant groups and high molecular weight (p.273, first paragraph).

It would have been obvious to one of skill in the art to use the polymalic acid polymer taught by Cammas to conjugate the targeting, prodrug, pore-forming, PEG, and reporter moieties taught by LaFleur. Cammas teaches that polymalic acid polymers allow for attachment of several functional or pendant groups to the polymer for delivery. LaFleur teaches the conjugation of prodrugs (antisense molecules targeting KDI), targeting modules such as antibodies and moieties for promoting penetration of the blood brain barrier, PEG, fluorescent reporter moieties, and pore-forming moieties and indicates that a preferred embodiment of the KDI compositions are formulated in a polymalic acid polymer. It further would have been obvious to make tyhe polymalic acid polymer of the claimed molecular weight because LaFleur teaches that the molecular weight may be modified to obtain the desired drug release. Provided the teachings of Cammas, one of skill in the art would immediately recognize that, of the polymers that can be used in the KDI compositions of LaFleur, polymalic acid polymers would be preferred because various moieties can be attached to the same polymer. Therefore, the claims would have been obvious to one of skill in the art at the time of the instant invention.

Claims 1-13 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFleur, et al. (10/29/2002, U.S. Patent 6,472,512) and Cammas, et al. (1999, Internat. J. Biol. Macromol., v.25:273-82, item 55 on 11/08/2007 IDS) (Cammas) as applied to claims 1-13 and 20 above, and further in view of Saito, et al. (2003, Adv. Drug Del. Rev., v.55:199-215, item 63 on 11/08/2007 IDS) (Saito).

Claims 1-13 and 20 are described in the preceding rejection. Claims 18 and 19 specify that the pro-drug molecular module is linked to the molecular scaffold by a linkage that is cleaved when the drug delivery molecule enters a cell, specifically a disulfide linkage.

The teachings of LaFleur and Cammas are indicated in the previous rejection. Neither LaFleur nor Cammas specifically teach linkage of the functional moieties to the scaffold by disulfide linkages.

Saito teaches that the incorporation of disulfide bonds in drug conjugates are designed to exploit differences in the reduction potential at different locations within cells (abstract). Saito teaches that a controlled cleavage and release of disulfide-bond-linked drug components can occur upon cell entry (p.200, section 1.2).

It would have been obvious to link the pro-drug of LaFleur to the polymalic acid scaffold with disulfide linkages because Saito teaches that such linkages allow for intracellular delivery of pro-drugs. The KDI antisense oligonucleotides of LaFleur, for example, exert their function intracellularly. Therefore, one of skill in the art would recognize that the disulfide bonds taught by Saito would be appropriate for linking the KDI antisense oligonucleotides to the polymalic acid polymer.

Claims 1-13, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFleur, et al. (10/29/2002, U.S. Patent 6,472,512) and Cammas, et al. (1999, Internat. J. Biol. Macromol., v.25:273-82, item 55 on 11/08/2007 IDS) (Cammas) as applied to claims 1-13 and 20 above, further in view of Summerton, et al. (1997, Nuc. Acid Drug Dev., v.7:187-95, item 38 on 11/08/2007 IDS) (Summerton).

Claims 1-13 and 20 are described above. Claim 21 specifies that the antisense molecule is a morpholino antisense molecule.

The teachings of LaFleur and Cammas are indicated in the previous rejection. LaFleur teaches that the KDI antisense oligonucleotides include modified oligonucleotides (column 143, line 58 to column 146, line 62). Neither LaFleur nor Cammas specifically teach a morpholino antisense molecule.

Summerton teaches the modified oligonucleotides, morpholino oligonucleotides, that afford the benefits of having very high efficacy and specificity, immunity to nucleases, good aqueous solubility, and low production costs (p.188).

It would have been obvious to one of skill in the art to incorporate morpholino antisense oligonucleotides for the modified antisense oligonucleotides taught by LaFleur because Summerton teaches the benefits of using such morpholino antisense oligonucleotides.

Claims 1-13, and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFleur, et al. (10/29/2002, U.S. Patent 6,472,512) and Cammas, et al. (1999, Internat. J. Biol. Macromol., v.25:273-82, item 55 on 11/08/2007 IDS) (Cammas) as applied to claims 1-13 and 20 above, further in view of Khazenzon, et al. (2003, Mol. Cancer Ther., v.2:985-94, item 47 on 11/08/2007 IDS) (Khazenzon).

Claims 1-13 and 20 are described above. Claim 21 specifies that the antisense molecule is a morpholino antisense molecule. Claims 22 and 23 specify that the antisense molecule targets α4-laminin.

The teachings of LaFleur and Cammas are indicated in the previous rejection. Neither LaFleur nor Cammas specifically teach a morpholino antisense molecule or an antisense oligonucleotide targeting α4-laminin.

Khazenzon teaches morpholino antisense oligonucleotides targeting α4-laminin (abstract). At page 993, third paragraph, Khazenzon discuss the use of the antisense oligonucleotides for treatment *in vivo* of brain gliomas.

It would have been obvious to formulate the antisense oligonucleotides of Khazenzon in the polymalic acid drug delivery molecule taught by LaFleur and by Cammas. LaFleur and Cammas teach the versatile nature of polymalic acid polymers and that antisense oligonucleotides and cell targeting moieties for traversing the blood brain barrier can be conjugated to the polymalic acid polymers. One of skill in the art would recognize that *in vivo* treatment of brain gliomas with α4-laminin-targeted antisense oligonucleotides as suggested by Khazenzon would require that the oligonucleotides be formulated for traversing the blood brain barrier and that the drug delivery molecules of LaFleur and Cammas would be readily adapted for such formulation. Thus, the claims would have been obvious at the time of the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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